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December 23, 1999

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 99D-3082; Draft Guidance, International Conference on Harmonization; Choice of Control Group in Clinical Trials, 64 *Federal Register* 51767-51780 (September 24, 1999)

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion. For these reasons, we are very interested in and well qualified to comment on then proposed draft guideline International Conference on Harmonization; Choice of Control Group in Clinical Trials.

Bristol-Myers Squibb offers the following comments on the draft guidance: International Conference on Harmonization: E10 Choice of Control Group in Clinical Trials. We believe these changes are required to clarify the intent in the guidance and achieve full harmonization in its interpretation.

General Comments

The document would greatly benefit from inclusion of a glossary to both minimize redundancy and ensure correct interpretation of the guideline. This would be particularly valuable for the more technical terms, e.g., equivalence, assay sensitivity, margin, noninferiority.

The guideline would benefit from an editing to remove redundant information both between sections. For example, much of the general description of each type of control included in Section 1 is repeated in section 2. We also note that information in the advantages and disadvantages parts of section 2 repeat information included in previous parts of their respective subsections.

99D-3082

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Relative Risk/Benefit Assessment

Several statements contained in the draft Guideline imply that a relative risk/benefit assessment, as demonstrated in active-controlled trials, could become a prerequisite for granting new drug approvals. We believe that introducing a benefit/risk assessment versus an established therapy requirement is counter current regulations and guidelines and the interest of Public Health. This requirement would adversely affect the scientific validity, cost, and duration of drug development, and discourage approvals or subsequent research on new therapies that could ultimately provide important therapeutic benefits. Therefore, we ask that the FDA pay special consideration to the following statements in the draft Guideline that could be seriously misleading:

> Paragraph 1.4.2. Comparative efficacy and safety:
> "*In some cases the focus of the trial is the comparison with another agent, not the efficacy of the test drug per se*".
>
> "*... the primary focus of such a trial is the comparison of treatments, rather than demonstration of efficacy*"...
>
> "*.. for the comparative trial to be informative concerning relative benefit and risk, the trial needs to be fair*"...
>
> Paragraph 2.4.6.2 Information Content.
> "*Active control trials also can, if properly designed, provide information about relative efficacy*".

Such statements could lead to the conclusion that a comparison of a test drug to another agent for the purpose of assessing the relative benefits and risks of a new drug versus an established therapy can become a requirement for registration. This interpretation appears to be supported by the following statement suggesting assessment of relative benefit is needed even if the intrinsic safety and efficacy of a new drug has been demonstrated in placebo-controlled studies.

> Paragraph 2.1.7.4. No comparative Information:
> "*Placebo-controlled trials lacking an active control give little useful information about comparative effectiveness, information that is of interest and importance in many circumstances*".

This concept goes far beyond the current requirement of establishing the safety and efficacy of a new agent. Indeed, placebo-controlled trials are useful in that they provide information on the full effect of the new agent in an untreated patient. As noted in the draft Guideline, active-controlled trials themselves can only demonstrate meaningful data on relative safety and efficacy, in some specific circumstances and under certain conditions.

The emphasis in the draft Guideline on trials that demonstrate relative risk/benefit is continued in the concluding Table 1 and Figure 1.

> Paragraph 3. Choosing the control group:
> "*Figure 1 and Table 1 provide a decision tree for choosing among different types of control groups. Although the table and figure focus on the choice of control to demonstrate efficacy, some designs also allow comparisons of test and control agents*".

Indeed, Figure 1 includes (without any hierarchy among options) active control trials as a possibility in all circumstances, even when placebo studies are feasible.

The draft ICH E10 Guideline extensively describes the scientific limitations of active-control study designs. We believe that such trials of new drugs must be reserved for those therapeutic conditions when circumstances do not allow for the use of more robust methodologies. Consequently, we feel strongly that the current ICH E10 draft Guideline needs to be revised in such a way that active-controlled studies are discussed only in terms of their ability to demonstrate safety and efficacy.

The active participation by FDA in the ICH process suggests their agreement with a requirement for demonstration of "relative risk/benefit". We understand that FDA's interpretation of this "guideline", as it affects the design of registration studies may differ from other regions participating in ICH. However, we want to emphasize that a requirement for "relative risk/benefit" in other ICH regions will affect clinical development programs for international registration and result in fewer placebo-controlled studies in NDAs and BLAs. Therefore, we strongly encourage FDA to advocate removal of text in the guideline emphasizing active-controlled studies to assess relative risk/benefit.

Noninferiority/Equivalence Trials

The guidance regarding "noninferiority/equivalence" trials requires clarification. As noted above, the present text would be greatly improved with an available glossary of these terms (i.e., noninferiority, equivalence) and other important terms used in the guidance (e.g., margin, sensitivity).

"Statistical equivalence" of two drugs is usually identified through demonstration that the drug effects do not differ more than some prespecified amount; one drug effect is within a minus delta or plus delta of the other. This approach is useful for bioequivalence. However, for clinical trials there generally is no need to constrain a new drug to an effect no more than delta greater than the active control. (There may be some exceptions where too great a response in associated with safety concerns). For this reason, the term "clinical equivalence" was developed and corresponded to a one-sided test, i.e., the new drug should not be more than delta worse than the active control.

Independent of equivalence testing, it has always been acceptable to predefine and analyze clinical trial data with a one-sided test of the following:

Hypothesis 1. The test drug effect is no more than delta worse than the comparator.

Hypothesis 2. The test drug is at least as good as the comparator (delta is zero).

Hypothesis 3. The test drug effect is superior to the comparator.

It is possible to design a trial where one tests Hypothesis 1 and, if significant, tests Hypothesis 3 using the same alpha. Thus, a trial can be designed to prospectively test for "clinical equivalence"/noninferiority and, if the data are supportive, test and demonstrate statistical superiority. (It should be noted that this two step analysis is not the same as testing for "statistical equivalence"). This approach should be identified in the guideline.

Regardless of the approach the guideline should specify that statistical support for Hypothesis 1 justifies a claim of "clinical equivalence" to the comparator rather than a claim of "noninferiority."

The former claims are more easily interpreted for the prescribing physician. Use of the term "clinical" in the "clinical equivalence" claim distinguishes the claim for the more robust equivalence, namely bioequivalence.

Specific Comments

1.0 Introduction

The use of the term "bias" in this section appears contrary to the technical definition identified in ICH E9 and the last paragraph of Section 1.2 of this draft. A control group cannot reduce "bias." Rather, a control group affects the statistical inferences that are possible.

1.1 General Scheme and Purpose of Guidance

These general comments omit considerations in selecting a control for demonstrating differences in "safety."

1.2 Purpose of Control Group

This first sentence in the first paragraph is overstated. Rather, it should be noted that the control group allows a relative comparison to the test drug.

1.3.3 Dose-response Concurrent Control

This section should be revised. The current text confuses the comparisons made in a fixed-dose dose-response design with a dose-response design including titration. The specific intended comparisons should be clarified.

1.3.6. Multiple-Control Groups

A three-arm trial (test drug, active drug, placebo) has multiple purposes and the two comparisons to placebo should be given the same weight. The comparison of the active drug to placebo is primarily an assumption check and not a primary analysis.

1.4.1 Evidence of Efficacy

This section fails to identify a dose-response study demonstrating a significant non-zero slope in the response as support for efficacy of the test drug.

1.4.2 Comparator Efficacy and Safety

The next to last paragraph should be deleted, since the important considerations affecting the interpretation of active controlled trials (e.g., patient population, dose) are covered in Section 2.4.

1.4.2.3 Selection and timing of endpoints.

We suggest the example with thrombolytics clarify that the drugs" reduce mortality but increase **hemorrhagic** stroke risk."

2.4.4 Usefulness of Active-Control Trials and Quality/Validity of Inference in Particular Situations

The first sentence requires clarification; how does a "study have inferential properties regarding the presence of efficacy equivalent to any other difference-showing trial?"

3.0 Choosing the Control Group

The last paragraph should be deleted. The text over simplifies the ease of designing an active-controlled study for demonstration of superiority.

Bristol-Myers Squibb appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

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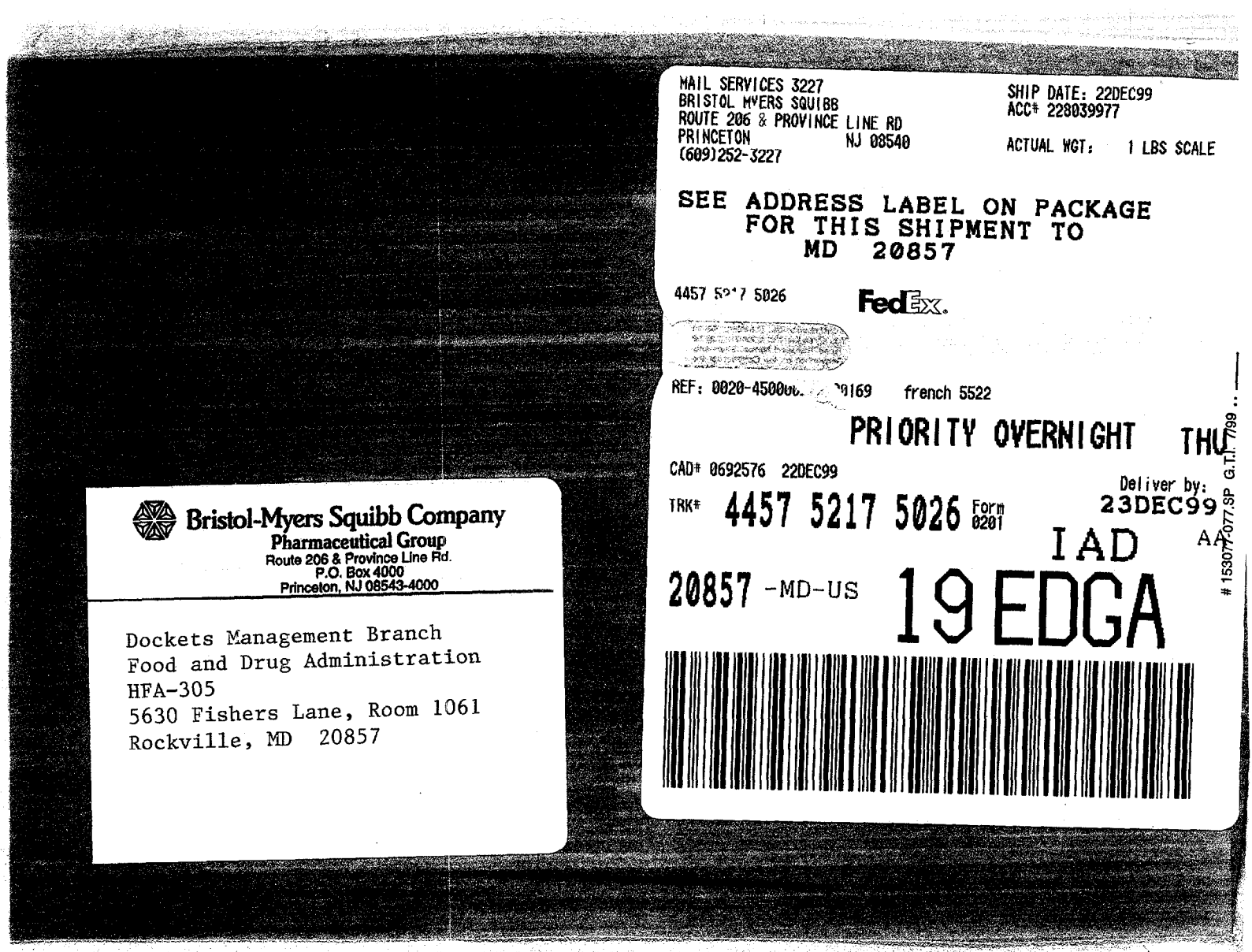

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